

REMARKS

This application is amended in a manner to place it condition for allowance.

Claim 1 is amended for the amendment may be found, for example, in paragraphs [0018], [0091], and Figure 1 of the published application.

Claims 2 and 4-14 are generally amended as to form.

Claim 3 is amended to recite "flat" in a manner as defined in the present application, for example, at paragraph [0075], Figure 3.

Claim 17 is amended for clarity in a manner consistent with Figures 12 and 13 and explained in paragraphs [0097], [0102], and [0130].

Claims 30-32 are new, and further define the meaning of "modified" cross-section, e.g., as shown in Figure 1.

Claims 15 and 16 are cancelled.

Claims 1-14, 17, and 30-32 remain pending in the application.

Claims 1-17 were rejected under 35 U.S.C. §112, first paragraph, for not complying with the written description requirement. This rejection is respectfully traversed for the reasons below.

The Official Action stated that it was unclear as to how the claim hollow fibers are formed.

The claims have been amended in a manner consistent with the written description to clarify the physical features of the fibers in the claimed device. Moreover, the method of obtaining the device of the present invention is described in original specification by the following steps (I), (II) and (III):

I. Obtaining a modified cross-section hollow fiber membrane. (See, e.g., [0105] of the published publication.)

A conventional hollow fiber has a cross-section that is the shape of a perfect circle, but in the present invention a modified cross-section hollow fiber is used ([0018]).

The conventional hollow fiber has inner and outer peripheral portions which are in the shapes of perfect circles and arranged concentrically. However, the hollow fiber of the present invention is intentionally deformed so that the shape of the cross-section is not a perfect circle, at least at the inner side of the hollow fiber, in order to make a distance from the arbitrary point of the cell aggregate (organoid) formed in the hollow portion to the nearest inner wall of a hollow fiber less than 75  $\mu\text{m}$ . The flat shape is particularly preferable ([0070]).

Moreover, the modified cross-section hollow fiber membrane has a substance permeability ([0082]).

The method of obtaining the modified cross-section hollow fiber membrane include a method for the formation of a

modified cross section simultaneously with the membrane formation and a method for deforming a hollow fiber membrane by subjecting the hollow fiber membrane to a mechanical processing after membrane formation([0107]).

The hollow fibers of the present invention are Press 100 of PE/EVAL and PP hollow fiber.

The features of the modified hollow fiber are shown in Table 1 of the specification.

II. Injecting a cell suspension into the hollow portion of the modified cross-section hollow fiber membrane. ([0109])

When filling a modified cross-section hollow fiber with cells of interest ([0017]), the concentration of the cell suspension is preferably  $2 \times 10^7$  cells/ml or less in order to attain a high density without damage to the cells ([0112]). Then, the dispersed cells are subjected to external forces such as centrifugal forces and hydrostatic pressures to allow a liquid element to be removed through filtration while filling a high cell density for incubation ([0111]).

III. Accumulating a high density of cells. ([0113])

After the cells are injected into the hollow portion of the hollow fiber membrane, in substantially the axial direction of the hollow fiber membrane, a centrifugal force of 5 to 1,500 G is applied for about 30 to 600 seconds to accumulate a high

density of cells ([0113]). In the case of using hydrostatic pressure, the hollow fiber injected with cells is set up, and then a hydrostatic pressure of 5 to 25 kPa is loaded in the hollow fiber for 4 to 120 hours ([0114]).

As mentioned above in reference to the method of obtaining the claimed device, the device of the present invention is obtained by providing a hollow fiber membrane whose cross-section is deformed in advance, filling a suspension of the cells of interest into the hollow portion of the membrane, removing liquid (water) utilizing the filtration activity of the membrane to attain a high density of cells, and forming the cell aggregates in the hollow fiber membrane.

The term "a distance from an arbitrary point of the cell aggregate to the nearest inner wall of the hollow fiber membrane is less than 75  $\mu\text{m}$ " means that a distance from any point of the cell aggregate (organoid) formed in the hollow portion to the (closest) inner wall of the hollow portion cannot be 75  $\mu\text{m}$  or more ([0091]). In other words, if the cross section of the hollow fiber membrane has a shape of flat or oval as shown in Fig. 3, the shorter diameter is less than 150  $\mu\text{m}$  (15  $\mu\text{m}$  or less in radius). This is illustrated in Figure A of the Appendix of this amendment. A hollow fiber membrane which has a cross-section of other shape than flat or oval can be used, as shown in Figure B of the Appendix.

Because cells are a few to several tens of  $\mu\text{m}$  in size, in general, if they are filled in the hollow fiber membrane at high density, it is clear that they cannot exist in a single layer but in two or more layers at whichever direction.

It is important to select proper dimensions in connection with the cross-section according to the shape of the cross section in order to obtain the device of the present invention. The actual conditions to achieve steps (II) and (II) are shown, for example, in reference example 1 of the specification.

Thus, in light of the above, one skilled in the art would have easily understood how to obtain the device of the present invention by referring to the instant specification.

Therefore, withdrawal of the rejection is respectfully requested.

Claims 1-17 were rejected under 35 U.S.C. §112, second paragraph, for being indefinite. This rejection is respectfully traversed for the reasons below.

The claims are amended to address the issues raised in the Official Action.

For example, the claims no longer recite "type", "characterized in that", and "arbitrary point".

The preamble is also amended to clarify the claimed features.

As to the recitation "modified cross section", this recitation means that the shape of the cross section is one other than the usual perfect circle. The claims are amended to be consistent with this meaning. Additionally, the new claims refer to the specific modified cross section shapes as defined in Figure 1.

With respect to the recitation "pore size", this is not the same as the inner diameter of the hollow membrane, as evidenced by the discussion of the inner diameter in [0018] and the discussion of both pore size and diameter in the Examples.

As to the term "flat", in Figure 3, the upper right figure is flat while the upper middle is oval, e.g., a "contact angle of 70 degrees or less". A method of measuring contact angle is described in [0075].

With respect to claim 17 in particular, claim 17 refers to features shown in Figures 12 and 13, and discussed in [0097], [0102], and [103]. That is, hollow fiber membranes are filled with the cells, and the liquid to be treated (the cells work as an artificial organ to treat the liquid) flows through the space between the wall of the container and the outside of those membranes. Some of the components of the liquid permeate into the hollow portions of the membranes to be treated.

Therefore, the claims are definite, and withdrawal of the rejection is respectfully requested.

Claims 1, 2 and 4-17 were rejected under 35 U.S.C. §102(b) as being anticipated by FUNATSU et al. U.S. 6,284,451 ("FUNATSU"). This rejection is respectfully traversed for the reasons below.

FUNATSU uses a conventional hollow fiber membrane with an unmodified cross-section, i.e., the shape is a perfect circle. FUNATSU fails to disclose or suggest modified cross-sections, which are shaped as deformed perfect circles, e.g., as claimed and illustrated in Figure 1 of the present application.

Therefore, withdrawal of the anticipation rejection is respectfully requested.

Claim 3 was rejected under 35 U.S.C. §103(a) as being unpatentable over FUNATSU. This rejection is respectfully traversed for the reasons below.

The position of the Official Action was that it would have been obvious to provide the hollow fiber of FUNATSU in flat form to enable placing fibers closer together in a smaller space.

However, according to the present invention, because the distance between the cell aggregates and the inner wall of the hollow fiber membrane is limited to less than a certain value, generation of a necrotized layer in the device is suppressed, and the effective utilization of the cells was achieved.

Contrary to the statement made in the Official Action, the present invention does not aim to place fibers closer

together in a smaller space, but to effectively use the cells without the necrosis by filling the cells in a hollow fiber membrane which has a modified cross section.

As discussed above with respect to the anticipation rejection, FUNATSU neither discloses nor suggests a cross section shape other than that of a perfect circle.

If a conventional hollow fiber membrane whose cross section is a perfect circle is used, and the diameter of the fiber is increased in order to increase the cells to be filled in the hollow portion, a necrotized layer is easily formed due to the shortage of nutrition, oxygen, etc. at the center of the hollow portion. Thus, only part of the cells which were filled in the hollow fiber was utilized. This leads to serious problems when the cells are rarely available (valuable). On the contrary, if the inner diameter is too small, the manufacture thereof becomes difficult. Further, an airlock or the like can be caused and sometimes affects the operation of uniformly filling the cells (See [0011]).

The claimed invention provides a smaller distance to the cells (cell aggregates) so that the necrosis be prevented as well as avoiding problems which accompanies the hollow fiber membrane with small diameter. FUNATSU does not teach or suggest the modified cross section of the hollow fiber membrane as well as the effects brought about by such a hollow fiber membrane.



FUNATSU discloses only a hollow fiber membrane whose diameter is 285µM, which corresponds to the control in Table 1. In Fig. 6, a big necrotic layer is observed at the center of the cell aggregates.

Therefore, claimed invention is not obvious over FUNATSU, and withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON

/Robert A. Madsen/  
Robert A. Madsen, Reg. No. 58,543  
209 Madison Street, Suite 500  
Alexandria, VA 22314  
Telephone (703) 521-2297  
Telefax (703) 685-0573  
(703) 979-4709

RAM/lk

**Appendix:**

The Appendix includes the following item:

- Figures A and B